Case Report Rapport de cas

Kidney injury in a dog following bee sting-associated anaphylaxis

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Abstract — This report describes a case of honeybee envenomation in a dog that developed anaphylaxis after being stung by approximately 10 bees. The dog subsequently developed acute kidney injury. The dog had a previous mild increase in blood urea nitrogen with normal creatinine, possibly indicating an insidious chronic renal degenerative process that went into acute decompensation at the time of bee envenomation.

Résumé — Lésion rénale chez un chien après l'anaphylaxie associée à une piqûre d'abeille. Ce rapport décrit un cas d'envenimement d'un chien qui a été piqué par environ 10 abeilles et a développé l'anaphylaxie puis une lésion rénale aiguë. Le chien avait eu une légère hausse antérieure de l'azote uréique du sang avec une créatinine normale, ce qui indique éventuellement un processus dégénératif rénal chronique insidieux qui s'est développé en une décompensation aiguë au moment de l'envenimement par les abeilles.

(Traduit par Isabelle Vallières)

Can Vet J 2017;58:265–269

Severe systemic allergic reactions in dogs living in North America most commonly occur because of an insect bite or sting, and the most clinically important encounters originate from insects belonging to the order Hymenoptera (1,2). The 3 groups of Hymenoptera most frequently responsible for physical symptoms relating to allergic reactions seen in veterinary hospitals are: Apidae (bees), Vespidae (hornets, wasps, and yellow jackets), and Formicidae (fire ants) (3). Although honeybees are comparably more docile than most of these venomous hymenopterans, they are very protective of their hives and they will attack humans or animals that pose a threat to their habitat. The venom in the sting can cause pathology ranging from local benign lesions to severe life-threatening systemic reactions. Honeybees are only able to sting once, as their barbed stinger catches in the victim's skin, pulling the stinging apparatus from the bee's body causing the bee to die. The venom sac continues to contract outside the bee's body and 100% of the venom is delivered within 60 s (4).

The main components of bee venom are: melittin, peptide 401 (mast cell degranulating peptide), phospholipase A_2, hyaluronidase, histamine, dopamine, acid phosphatase, apamine, and norepinephrine (5), with melittin being the main component of venom both by amount and lethality. Melittin, acting synergistically with phospholipase A_2, disrupts cell membranes of certain mammals and causes lysis of erythrocytes, leukocytes, platelets, myocytes, and vascular endothelium (6). This in turn releases myoglobin and hemoglobin, which have been linked to acute tubular necrosis and acute kidney injury (AKI) in humans and other species, including dogs (7–9). Melittin has also been associated with acute myocardial ischemia, producing arrhythmias (6,10). Peptide 401 causes mast cells to release histamine and vasoactive amines causing vasodilation (1). Hyaluronidase causes breakdown of connective tissue and promotes further uptake and spread of venom (6).

Reactions to insect envenomation fall into 5 main categories: local pain and swelling, larger regional reaction, anaphylactic reaction, serum sickness (delayed-type hypersensitivity) occurring 3 d to 2 wk after envenomation, and a rare delayed toxic reaction in humans seen within 24 h after severe envenomation characterized by hemolysis, coagulopathy, hepatopathy, thrombocytopenia, and disseminated intravascular coagulation (DIC) (1,11). Anaphylaxis, a Type I (immediate) hypersensitivity mediated by IgE, is the most serious complication in dogs. Anaphylactoid reactions resemble anaphylaxis but are independent of IgE and, although compounds have been identified that act directly on cell membranes of mast cells, the exact mechanism for these reactions remains unclear (12). Both anaphylactic and anaphylactoid reactions are similar in their appearance and treatment, and consequently the terms are often used interchangeably (12). The combined effects of severe envenomation and anaphylaxis include intravascular hemolysis, rhabdomyolysis, hepatopathy, cardiac damage, AKI, immune-mediated hemolytic anemia (IMHA), immune-mediated thrombocytopenia (IMTP), and DIC (1,10,11,13–15). Acute lung injury/acute respiratory distress syndrome (ALI/ARDS) as defined by

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acute onset of bilateral pulmonary infiltrates without evidence of left atrial hypertension and subsequent hypoxemia has been reported in dogs and substantiated using advanced imaging and pulmonary function tests (16). This paper describes a dog envenomated by honeybees resulting in acute kidney injury.

Case description

A 9-year-old intact female mixed breed dog weighing 10.8 kg was presented to the referring veterinarian after being found unresponsive in the owner's truck with at least 10 bees, some of which were dead. Honeybees used for crop pollination had been released within the previous hour near the truck which was parked under a tree with the windows down. Ten months before this incident, routine blood test results from the dog showed a mild increase in blood urea nitrogen (BUN) with a normal creatinine [BUN 19.2 mmol/L, reference range (RR): 3.2 to 11.0 mmol/L; creatinine 114.4 μmol/L, RR: 44 to 132 μmol/L] and mild anemia (hematocrit, HCT, 0.34, RR: 0.38 to 0.56) without appreciable dehydration or clinical signs of kidney disease. No further testing was done at that time so, while a mild chronic kidney disease (CKD) (IRIS Stage 1) at the time of the envenomation is conceivable, it cannot be confirmed. An additional important historical finding for this dog was diagnosis of a congenital spinal malformation resulting in hind limb paralysis and urinary incontinence along with significant muscle atrophy and a resulting body condition score (BCS) of 3/9. The dog had no other physical abnormalities or clinical signs of illness leading up to the current incident.

The dog was presented to the referring veterinarian within 30 min of envenomation. It was apneic, bradycardic (heart rate: 20 beats/min), and was unresponsive to noxious stimuli. Emergency medical treatment consisted of intubation and manual ventilation, epinephrine 0.02 mg/kg body weight (BW), IV, and diphenhydramine (Diphenhydramine injection; West-Ward, Eatontown, New Jersey, USA), 7 mg/kg BW, IV and IM. Blood pressure measurement was too low to be read by Doppler. A 4 mL/kg BW bolus of hydroxyethyl starch (Hetastarch; Teva Parental Medicines, Irvine, California, USA) and 20 mL/kg BW bolus of lactated Ringer's solution (LRS) were given, in addition to dexamethasone SP (Bimeda-MTC Animal Health, Cambridge, Ontario), 0.22 mg/kg BW, IV. After 10 min of resuscitation the dog began breathing spontaneously with a hemoglobin saturation (SpO_2) of 94% on 100% oxygen. After 20 min, the dog became responsive and was able to lift its head and swallow. The dog was placed in an oxygen cage while receiving a maintenance IV dose of LRS of 50 mL/kg BW, q24h. The dog then developed bloody diarrhea. Metronidazole (Baxter Healthcare, Deerfield, Illinois, USA), 10 mg/kg BW, IV, and famotidine (West-Ward), 0.7 mg/kg BW, IV, were administered. After several hours of treatment by the primary veterinarian, the dog was referred to a tertiary emergency veterinary hospital.

When the dog arrived at the referral hospital, it was obtunded and severely hypotensive (blood pressure measurement too low to be read). It had a respiratory rate of 104 breaths/min with increased effort, and cyanotic mucous membranes. The dog had hematochezia that became melenic within 1 h. It was given oxygen by facemask and LRS (20 mL/kg BW over 10 min). Soon after receiving the fluids the systolic blood pressure increased to 156 mmHg and the mentation improved, as evidenced by the dog being able to lift its head and respond to physical touch and sound. The dog was then moved to an oxygen cage with a fraction of inspired oxygen (FiO_2) of 0.4 and placed on LRS at 35 mL/h, which was maintained throughout the remainder of the hospitalization. The following medications were subsequently administered over the next 2 h: ampicillin with sulbactam (Unasyn; West-Ward), 30 mg/kg BW, IV, pantoprazole (Akorn, Lake Forest, Illinois, USA), 1 mg/kg BW, IV, maropitant citrate (Zoetis, Kalamazoo, Michigan, USA), 1 mg/kg BW, SQ, sucralfate (Sanofl-aventis, Kansas City, Missouri, USA), 500 mg, PO, and diphenhydramine (Benadryl; McNeil Consumer Healthcare, Fort Washington, Pennsylvania, USA), 2 mg/kg BW, PO, q12h. Blood test results (Critical Care Xpress Stat Profile; Nova Biomedical, Waltham, Massachusetts, USA) showed metabolic acidosis, hypoglycemia, and azotemia (Table 1). Another venous blood gas analysis taken 7 h later revealed unchanged kidney values but resolving mild metabolic acidosis and normoglycemia (Table 1). The dog remained stable overnight. Its heart rate ranged between 88 and 115 beats/min with occasional ventricular premature contractions (VPC's), systolic blood pressure measurements ranging between 120 and 155 mmHg, and respiration rate that ranged between 28 and 36 breaths/min. Due to the dog's congenital spinal malformation, incontinence, and agitation on manipulation, and with the risks of sedation required for urinary catheter placement, urinary output was not accurately monitored. A urine sample was not collected at this time for the same reasons.

Table 1. Blood gas values, packed cell volume (PCV), and total solids (TS) in a dog with bee sting envenomation

	On presentation	7 hours later	40 hours later	Reference range
pH	7.28	7.38	7.44	7.33 to 7.44
pCO_2	32.2	27.8	26.4	35 to 40 mmHg
pO_2	68.1	70.9	91.6	32 to 62 mmHg
Glucose	4.12	5.33	5.95	4.78 to 6.1 mmol/L
Lactate	3.0	0.8	0.7	0.4 to 1.5 mmol/L
BUN	19.6	18.5	16.1	3.57 to 10.7 mmol/L
Creatinine	185.64	176	140.8	70.4 to 132 μmol/L
HCO_3	15.5	16.7	18.3	18 to 27 mmol/L
TCO_2	16.5	17.5	19.1	19 to 28 mmol/L
PCV	51			37% to 55%
TS	64			51 to 78 g/L

BUN — blood urea nitrogen.

The following day oxygen treatment was discontinued and diphenhydramine 2.5 mg/kg BW was switched to the oral route q12h. An intermittent supraventricular tachycardia with occasional VPC's occurred and spontaneously disappeared. A hemogram showed leukocytosis with neutrophilia and lymphopenia along with a HCT of 0.39 (Table 2). The serum chemistry showed elevated liver enzyme levels, azotemia, and mild hypoalbuminemia (Table 2). Both samples showed mild hemolysis despite careful collection but the urine pads showed no gross evidence of pigmenturia.

The dog was cardiovascularly stable and continued to improve clinically on day 2 (last day of hospitalization at the owner's request). Systolic blood pressure measurement ranged from

Table 2. Complete blood cell count and blood analysis for the dog on the second day of hospitalization and at the 3-day re-check at the referral hospital

	Results (day 2)	Results (3-day recheck)	Reference range
WBC	22.13	20.23	5.0 to 13.0 × 10^9/L
HCT	0.39	0.41	0.4 to 0.56
MCV	70.2	68.1	64.0 to 74.0 fL
MCH	23.1	23.7	22.0 to 26.0 pg
Plasma protein	55	66	51 to 78 g/L
Neutrophils	18	12	2.7 to 8.9 × 10^6/L
Lymphocytes	0.88	2.0	0.9 to 3.4 × 10^6/L
Platelets	325	375	134 to 396 × 10^9/L
ALP	118	79	8 to 114 U/L
ALT	920	359	18 to 64 U/L
AST	988	32	15 to 52 U/L
Albumin	24	2.7	29 to 38 g/L
Total protein	55	63	56 to 65 g/L
BUN	18.2	44.2	2.8 to 8.9 mmol/L
Creatinine	238.6	300.5	53 to 149 μmol/L

WBC — white blood cells; HCT — hematocrit; MCV — mean corpuscular volume; MCH — mean corpuscular hemoglobin; ALP — alkaline phosphatase; ALT — alanine aminotransferase; AST — aspartate aminotransferase; BUN — blood urea nitrogen.

140 to 210 mmHg and enalapril (Wockhardt USA, Parsippany, New Jersey, USA), 0.25 mg/kg BW, PO, q12h, was added. Urine output was estimated by weighing urine pads, which indicated normal urine volume. A blood gas analysis performed at discharge showed improved azotemia (Table 1). Treatment at home was to consist of amoxicillin with clavulanic acid (Clavamox; SmithKline Beecham Pharmaceuticals, Philadelphia, Pennsylvania, USA), 23 mg/kg BW, enalapril, 0.23 mg/kg BW, and omeprazole (DexcelPharma Technologies, Yokneam, Israel), 0.9 mg/kg BW, all PO, q12h.

The dog returned 3 d later for a recheck. Its time at home showed a steady improvement in all aspects of the daily routine while receiving the medications as directed. The dog was voluntarily eating small amounts of food, becoming more interactive, and its stool was returning to a normal color and consistency. The dog's body weight was maintained at 10.8 kg and the chest auscultated normally. The hemogram showed improvement but still showed a leukocytosis, and the serum chemistry showed improved albumin and liver enzyme parameters but worsening azotemia (Table 2). A urinalysis showed isosthenuria (specific gravity: 1.014) with an unremarkable sediment and trace protein along with a mildly elevated urine protein:creatinine ratio (UPC: 1.1). The owner was persuaded to hospitalize the dog for overnight IV fluid treatment out of concern for premature discontinuation of treatment 3 d earlier. This was accomplished with LRS at a rate of 125 mL/kg BW per day. Due to the history of arrhythmias, a cardiology consultation, which included an echocardiogram, was done with the results showing no structural or rhythm abnormalities. During the dog's overnight stay mean arterial pressure (MAP) ranged from 107 to 111 mmHg, and the urine output was again estimated as adequate by weighing the urine pads. The dog was transferred to the referring veterinarian the following morning for continued IV fluids at the owner's request.

The patient did well at home over the next few months but slowly lost weight due to progressive kidney disease. Home maintenance treatment consisted of subcutaneous fluids given daily and a kidney diet (Science Diet K/D; Hills Pet Food, Topeka, Kansas, USA) mixed with an additional dog food diet (Pro Plan Focus Adult Sensitive Skin and Stomach Formula Dog Food; Nestle Purina, Wilkes-Barre, Pennsylvania, USA). The serum liver enzyme values became normal while the azotemia significantly worsened (BUN: 64.26 mmol/L, RR: 3.57 to 7.14 mmol/L, creatinine 618.8 μmol/L, RR: 44 to 159.1 μmol/L) along with appearance of severe hyperphosphatemia (5.55 mmol/L, RR: 0.8 to 2.19 mmol/L) when checked almost 3 mo after the bee sting envenomation.

The last recheck with the referring veterinarian was done 6 mo after the bee sting incident. Daily subcutaneous fluid administration had been given at home since leaving the referral hospital, with these treatments becoming significantly reduced by the 3-month recheck and then subsequently increased. Although blood testing at the time of the 6-month recheck showed marked azotemia (BUN 33.2 mmol/L, creatinine 371.28 μmol/L) and hyperphosphatemia (2.97 mmol/L; RR: 0.8 to 2.19 mmol/L) these values had improved from those done 3 mo previously. Blood pressure and urinalysis were not done but the most recent level of azotemia based on serum creatinine level showed the dog to be in IRIS Stage 3.

Discussion

The dog herein initially had anaphylactic shock due to bee stings and soon afterward was found to have sustained significant acute kidney injury. Moreover, with the blood test results 1 y earlier, it is possible that this case actually represents an acute or chronic kidney injury but more substantiating evidence would be required to assert this definitively. Anaphylaxis and acute kidney injury have both been documented in South American dogs following bee stings from Africanized honeybees (10). To our knowledge this is the first report of kidney injury following honeybee stings in North America. This dog was documented as having mild to moderately elevated BUN and normal creatinine almost 1 y prior to this incident. At that time it is possible that the dog was in IRIS Stage 1 with a lower than expected creatinine level as a consequence of significant muscle atrophy secondary to the rear limb paralysis and/or due to the dog's diet that incorporated table food, including high protein meats. No blood tests, urinalysis, urine culture, or imaging were done subsequently until the recent hospitalization and therefore pre-existing chronic kidney disease cannot be confirmed. Following the bee sting envenomation, the dog developed significant kidney injury, resulting in the patient progressing to a stable IRIS Stage 3 within a few months after the envenomation. In this case it is possible that the creatinine levels were artificially low due to the dog's muscle atrophy. It is possible that the kidney disease would be diagnosed as more advanced based on the IRIS staging system in a dog with a normal body condition. The kidney injury in this patient could have been caused by prolonged hypotension secondary to anaphylaxis along with direct nephrotoxic effects of the venom (7,17). Additionally, in light of the potential for angiotensin-converting-enzyme

(ACE) inhibitors to negatively affect the kidney when there is pre-existing reduced renal perfusion, the selection of this drug might have been a confounding factor to the dog's already compromised renal function. The kidney tubular degeneration and necrosis in this dog can be associated with direct toxicity of the venom in direct contact with the tubules, myoglobinuria and hemoglobinuria (although there was no evidence of gross pigmenturia), as well as hypotension creating an ischemic-toxic effect (10). In a retrospective study involving 19 dogs that died due to intoxication from multiple Africanized bee stings, all of the dogs were found to have kidney degeneration and tubular necrosis. This was associated with red or brown pigments, which formed intratubular cylinders and/or accumulated within the tubular epithelial cells, different from what would be expected in purely hypotension related kidney injury. Additional findings were focal areas of interstitial fibrosis (4/19) and glomerular atrophy (3/19) (10).

Anaphylaxis to Hymenoptera stings is a Type 1 IgE-mediated acute reaction that occurs within minutes of introduction of the venom. The reaction occurs when the animal has been previously exposed to the foreign antigen (Ag), stimulating B-cells to create IgE antibody-secreting plasma cells. These IgE antibodies then attach to Fc receptors on the surface of tissue mast cells and circulating basophils, which is termed sensitization. When the venom is subsequently reintroduced, the Ag attaches to the membrane bound IgE on sensitized cells and cross links the antibodies causing degranulation and release of pharmacologically active mediators such as histamine, serotonin, heparin, prostaglandins, leukotrienes, and platelet-activating factor (3,18). Although anaphylaxis occurs very quickly, late phase reactions known as biphasic reactions have been documented to occur in up to 20% of human patients (19). These reactions are reoccurrence of symptoms, delayed by up to 8 h after resolution of the initial symptoms (19). Diphenhydramine was administered to our patient for 24 h in an attempt to prevent this biphasic reaction.

The borderline low hematocrit was most likely caused by hemodilution from fluid resuscitation and continued fluid therapy along with the loss of blood into the digestive tract due to a severe hypotensive episode and "shock gut" syndrome. Hemolysis (as reported by the laboratory) and anemia were both found early in the course of hospitalization of this dog. Acute intravascular hemolysis has been described in cases of bee sting envenomation and is believed to be caused by cell membrane interruption by melittin and phospholipase A_2 components of the venom (10,17); however, given the lack of gross pigmenturia, we have insufficient evidence to support this as a cause of the mild anemia or kidney injury in this case. The anemia along with hypoproteinemia could both be due to gastrointestinal blood loss that occurred shortly after hospitalization. The mild hypoglycemia and the leukocytosis can be related to the melena and the possible association of mucosal barrier disruption with bacterial transmigration and sepsis early in the treatment period.

Melena is not uncommon in hypotensive animals and has been reported and accounted for by direct venom toxicity coagulopathy (10,20,21), which in this case could be related to the anaphylaxis and prolonged hypotension causing mucosal injury and hemorrhage. No coagulation testing was done for this patient, and the melena resolved within 24 h. Since there were no other coagulopathy specific signs such as excessive bleeding from blood sampling sites and IV catheter or cutaneous signs, it is unlikely that a coagulopathy was the cause of the melena. However, a coagulation evaluation would have been justified to identify any abnormalities compatible with DIC (prolonged partial thromboplastin time, prolonged prothrombin time, hypofibrinogenemia, and the detection of fibrin split products) because some of these parameters can be abnormal without clinical signs.

Soon after presentation to the referring veterinarian following envenomation, supraventricular tachycardia and ventricular premature contractions were noted and resolved spontaneously. Abnormal liver enzyme test results and cardiac arrhythmias have been noted in human and veterinary medical literature and attributed to hepatocyte and cardiomyocyte necrosis resulting from direct toxic effects of the venom, in particular melittin and phospholipase A_2 (1,5,10,15,20–23). Additionally, local ischemia, secondary to hypotension and hypovolemia are also considered important contributing factors.

Signs of bee sting envenomation are most commonly associated with the skin, gastrointestinal, cardiac, respiratory, neurologic, and ocular systems. In the cat, the respiratory and gastrointestinal systems are most often affected, but in the dog signs most frequently involve the skin and gastrointestinal systems (18). Treatment for all victims consists of intravenous fluids, oxygen supplementation, epinephrine, corticosteroids, antihistamines, and analgesics (if needed). Epinephrine continues to be the most important life-saving treatment in anaphylaxis because of its prevention of mast cell degranulation, its ability to cause vasoconstriction and increased blood pressure and heart rate, bronchodilatation, and maintaining endothelial integrity. Risk factors for severe complications following Hymenoptera envenomations are not noted in veterinary medicine. In human medicine with a larger population of patients with cardiovascular disease, treatment with beta-blockers or angiotensin converting enzyme (ACE) inhibitors at the time of envenomation is known to worsen the risk of complications (3). These drugs can potentiate the negative effects of the mast-cell mediators, prevent the breakdown of the neuropeptides and bradykinin released from mast cells, and block the effects of epinephrine used to treat the patient (3). In humans, continued hospitalization even after successful treatment for the first 24 h may be considered in order to monitor for biphasic and delayed type hypersensitivity reactions (19,24). A biphasic reaction was reported in a dog which developed anaphylaxis following a massive bee sting envenomation (16). That dog was treated and released the same day after successful response to treatment but within 48 h returned because of severe respiratory distress, vomiting, and restlessness and was found to have developed ARDS which was believed to have been due to the bee envenomation 3 d earlier. In this case we had advised further hospitalization with supportive care and treatment in the face of continued azotemia, but the owner declined. The owner and veterinary staff were in repeated contact after the patient left the hospital. The updates from home described the patient as symptomatically

improved prior to the 3-day recheck, but this short improvement was subsequently followed by a worsening azotemia. This emphasizes the need for longer duration of hospitalization and further testing when renal function is compromised.

This report describes an uncommon but important aspect of Hymenoptera envenomation and raises concerns that are not typically part of routine client education, especially for potentially high-risk dogs with existing kidney disease, co-existing heart disease and cardiac medications, liver disease, advanced age, and even those pets that have difficulty with ambulation as in this case. We now have an expanding population of aging patients that fall into high-risk categories for complications secondary to insect bite envenomation. There are several shortcomings in this case including the lack of urine sampling, the lack of any overt hemolysis, the uncertainty of pre-existing CKD, and the inability to observe the dog in the hospital for a longer period of time. Nevertheless the case serves to illustrate the important pathophysiology that can occur with honeybee envenomation. With consistent findings of hepatic, cardiac, and renal injury in case reports (10,14–16,18,20–22) involving Hymenoptera envenomations as well as concerns for cardiovascular medications that enhance the effects of the venom and diminish the effects of epinephrine, a cornerstone medication for anaphylaxis, clinician awareness, and owner education could prove invaluable to many patients.

This dog's previous mild increase in BUN with normal creatinine could have represented an insidious chronic renal degenerative process that went into acute decompensation at the time of bee envenomation. In light of this, owners of pets that have pre-existing hepatic, cardiac, and/or renal disease should be made aware of the potential complications that are associated with Hymenoptera stings. Although research is ongoing in the area of antivenom, mellitin-binders, antagonists to mast-cell mediators, and anti-melittin antibodies, none of these therapies are currently available to veterinary patients. Avoidance and education strategies that are commonly used in humans can be applied to veterinary patients, and are therefore our best proactive approach to this potentially deadly emergency. CVJ

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